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EXAMINER	
FRONDA, CHRISTIAN L	
ART UNIT	**PAPER NUMBER**
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/975,813	MILLER ET AL.	
	Examiner	Art Unit	
	Christian L. Fronda	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *26-30 and 33-52* is/are withdrawn from consideration.

5)☒ Claim(s) *3,5,6,24 and 25* is/are allowed.

6)☒ Claim(s) *1,2,4,7-23,31,32 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-53 are pending in the application. Claims 26-30 and 33-52 have been withdrawn from consideration.

2. Claims 1-25, 31, 32, and 53 are under consideration in this Office Action. New rejections and new grounds of rejection are presented in the instant office action.

3. The objection to the disclosure has been withdrawn in view of applicants' submission of a complete copy of the "Application Data Sheet".

4. The rejection of claims 1-25, 31, and 32 under 35 USC 101 as being directed to non-statutory subject matter has been withdrawn in view of applicants' amendment to the claims filed on 11/16/2005.

5. The rejection of claims 15-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for reciting the phrase "product peptide" has been withdrawn in view of applicants' amendment to the claims filed on 11/16/2005.

6 The rejection of claim 3 under 35 U.S.C. 102(b) as being anticipated by Doege et al. (J Biol Chem. 1991 Jan 15;266(2):894-902; and Accession A39086. 10-Sep-1999) has been withdrawn in view of applicants' amendment to claim 3 which is now directed toward an isolated aggrecan peptide fragment consisting of amino acids 1-40 of SEQ ID NO: 1

7. The rejection of claim 5 under 35 U.S.C. 102(b) as being anticipated by Hering et al. (Accession P13608. 01-JAN-1990) has been withdrawn in view of applicants' amendment to claim 5 which is now directed toward an isolated aggrecan peptide fragment consisting of amino acids 1-40 of SEQ ID NO: 2.

8. The rejection of claims 6 under 35 U.S.C. 102(b) as being anticipated by Antonsson et al. (Accession A34234 20-March-1992) has been withdrawn in view of applicants' amendment to claim 6 which is now directed toward an isolated aggrecan peptide fragment consisting of amino acids 1-40 of SEQ ID NO: 3.

Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly

claiming the subject matter which the applicant regards as his invention.

10. Claims 31, 32, 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 31 and 32 recite the limitation "wherein the P1 amino acid residue" in line 1 of each claim. There is insufficient antecedent basis for this limitation in the claim.

In claims 31 and 32, the phrase "ADMP-sensitive Glu^{373}-Ala^{374} bond" renders the claims vague and indefinite because it is not clear if applicants are actually referring to SEQ ID NO: 1. The Sequence Listing discloses that SEQ ID NO: 1 consists of only 40 amino acids. It is uncertain as to what specific bond between amino acid residues is being referred to by the phrase "ADMP-sensitive Glu^{373}-Ala^{374} bond". Appropriate correction is requested.

Claims 53 recites the limitation "wherein said numbering" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Claim 53 is vague and indefinite because the specific SEQ ID NO of the referenced "human aggrecan protein" has not been recited. It is uncertain as to what specific bond between amino acid residues is being referred to by the phrase "Glu^{373}-Ala^{374} , E^{1545}-G^{1546}, E^{1714}-G^{1715}, E^{1819}-A^{1820}, and E^{1919}-L^{1920}". No corresponding SEQ ID NO of the amino acid sequence is recited where the human aggrecan protein may be SEQ ID NO: 1, SEQ ID NO: 3, or any other amino acid sequence. Appropriate correction is requested.

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1, 2, 8-23, 31, 32, 53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants' arguments filed 11/16/2005 have been fully considered but are not persuasive. Applicants' position is that since the claims are amended to recite "aggrecan" and "fragment", then the amendments obviate the rejection. The examiner respectfully disagrees for reasons of record as supplemented below.

In the evaluation of the claims for compliance with the written description requirement of 35 U.S.C. 112, of particular relevance is 66 FR 1099, Friday, January 5, 2001,which states:

> "*Eli Lilly* explains that a chemical compound's name does not necessarily convey a written description of the named chemical compound, particularly when a genus of compounds is claimed. *Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1405. The name, if it does no more than distinguish the claimed genus from all others by function, does not satisfy the written description requirement because "it does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. *Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1406. Thus *Eli Lilly* identified a set of circumstances in which the words of the claim did not, without more, adequately convey to others that applicants had possession of what they claimed." (see p. 1100, 1st column, line 47 to 2nd column, line 2).

The claims are genus claims encompassing many aggrecan peptide fragments of any function, amino acid sequence, and structure having any ADMP-susceptible cleavage site of any amino acid sequence and structure. The scope the genus claims includes many peptides with widely differing structural, chemical, and physical characteristics. Furthermore, the genus is highly variable because a significant number of structural differences between genus members exists.

While the specification discloses SEQ ID NOs: 1-6; the recitation of the name "aggrecan peptide fragment comprising a specific ADMP-susceptible cleavage site" does not define any structural features and amino acid sequences commonly possessed by the genus. Furthermore, the specification does not describe and define any structural features and amino acid sequences commonly possessed by the genus. Thus, one skilled in the art cannot visualize or recognize the identity of the members of each genus for use in the claimed method.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definitions, such as the structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v, Eli Lilly and Co.* 43 USPQ2d 1398 (Fed. Cir. 1997), quoting *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe the genus of genetic materials, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g. structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these. Therefore, the instant claims are not adequately described.

In view of the above considerations, one of skill in the art would not recognize that

applicants were in possession of a genus of aggrecan peptide fragments of any function, amino acid sequence, and structure having any ADMP-susceptible cleavage site of any amino acid sequence and structure.

13. Claims 1, 2, 7-23, 31, 32, and 53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated human aggrecan peptide consisting of the amino acid sequence of SEQ ID NO:1 or SEQ ID NO: 3, does not reasonably provide enablement for any aggrecan peptide from any source or peptide fragment having any function, amino acid sequence, and structure comprising or an amino acid sequence that is 80% identical to amino acids 1-40 of SEQ ID NO: 1 or SEQ ID NO: 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants' arguments filed 11/16/2005 have been fully considered but are not persuasive. Applicants' position is that the amendment filed 11/16/2005 obviates the rejection. The examiner respectfully disagrees for reasons of record as supplemented below.

As stated in the previous Office Action dated 07/14/2005 and further explained here, the nature and breadth of the claims encompass any peptide or peptide fragment of any function, amino acid sequence, and structure comprising an amino acid sequence that is 80% identical to amino acids 1-40 of SEQ ID NO: 1 or SEQ ID NO: 3. The specification provides guidance and examples for making a peptide consisting of the amino acid sequence of SEQ ID NO:1 or SEQ ID NO: 3. However, knowledge regarding the biological utility of the claimed peptides and the specific amino acid residues to change without affecting biological activity of the claimed peptides or peptide fragment is lacking.

The amount of experimentation to determine the biological activity the specific amino acid residues to change without affecting biological activity of the claimed peptides or peptide fragment is enormous and undue. Such experimentation entails searching a vast number of biological sources from which to isolate the peptide or peptide fragment; searching and screening for a biological activity of the peptide; and screening and searching for any amino acid in SEQ ID NO: 1 or 3 to change (amino acid insertion, deletion, addition, substitution, or combinations thereof) that does not affect biological activity in order to make an amino acid sequence that is 80% identical to SEQ ID NO: 1 or 3. General teaching regarding screening and searching for the claimed invention is not guidance for making the claimed invention. Thus, the amount of experimentation to determine the specific biological function of the claimed peptides as well as their biological utility is undue. Dependent claim 8 is also rejected because it does not correct the defect of claim 4 or 7.

Claim Rejections - 35 U.S.C. § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1, 15, and 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Fosang et al. (FEBS Lett. 1996 Feb 12;380(1-2):17-20 [reference of record]; and GenBank Accession NP_037359 and NP_001126 [references of record]) as evidenced by Fosang et al. (Biochem. J. (1989) 261, 801-809; PTO 892).

Applicants' arguments filed 11/16/2005 have been fully considered but are not persuasive. Applicants' position is that the references do not teach an ADMP-susceptible peptide fragment. The examiner respectfully disagrees for reasons of record as supplemented below.

The teachings of Fosang et al. (1996) stated in the previous Office Action are reproduced here. Fosang et al. teach the aggrecan G1-G2 peptide substrate which was cleaved by collagenase (MMP-13) into peptide products (85 kDa, 75 kDa, and 50 kDa) at a position corresponding to the VKP_{384}|VFE site of aggrecan (see entire publication especially pp. 19, section *3.3 Digestion of G1-G2 with MMP-13* to section *3.4 N-terminal sequence analysis of an MMP-13 digestion product*). Furthermore, the attached reports for GenBank Accession NP_037359 and NP_001126 show the amino acid sequence of the said peptide substrate.

Although the claims now recite "An isolated peptide fragment", this does not obviate the prior art rejection. The said aggrecan G1-G2 peptide substrate taught by Fosang et al. is the isolated N-terminal fragment of cartilage proteoglycan protein core that was obtained after mild trypsin digestion of purified proteoglycan aggregates (see reference number [34]: Fosang et al. Biochem. J. (1989) 261, 801-809 (this reference is attached to the instant office action)). Thus, the reference teaching anticipates claim 1 since the aggrecan G1-G2 peptide was cleaved by MMP-13 (deemed to be aggrecan degrading metalloprotease (ADMP) because it is a metalloprotease that cleaved the said aggrecan G1-G2substrate); and the said aggrecan G1-G2 substrate contains the ADMP-susceptible cleavage site at a position corresponding to the VKP_{384}|VFE site of aggrecan.

Since the said aggrecan G1-G2 substrate was cleaved at the position corresponding to the VKP_{384}|VFE site of aggrecan, then the one of the proteolytically cleaved peptide products would inherently have amino acids from the N-terminus through P1 of the ADMP-susceptible cleavage bond and the other cleaved peptide product would have amino acids from the P1' of the ADMP-susceptible cleavage bond through the C-terminus. Thus, the reference teachings anticipate claims

15 and 16.

16. Claim 4 stands rejected under 35 U.S.C. 102(b) as being anticipated by Doege et al. (J Biol Chem. 1991 Jan 15;266(2):894-902; and Accession A39086. 10-Sep-1999 [references of record]).

Applicants' arguments filed 11/16/2005 have been fully considered but are not persuasive. Applicants' position is that the reference does not teach the claimed isolated aggrecan peptide fragment. The examiner respectfully disagrees for reasons of record as supplemented below.

As stated in the previous Office Action, Doege et al. teach a peptide comprising amino acids 1-40 of SEQ ID NO: 1 (see enclosed alignment). The claim as amended does not obviate the rejection since the claim still recites the phrase "comprising a sequence of amino acids". Thus, the reference teaching anticipates claim 4 which is directed toward a peptide comprising a sequence that is at least 80% identical to amino acids 1-40 of SEQ ID NO: 1.

17. Claim 7 stands rejected under 35 U.S.C. 102(b) as being anticipated by Antonsson et al. (Accession A34234 20-March-1992).

Applicants' arguments filed 11/16/2005 have been fully considered but are not persuasive. Applicants' position is that the reference does not teach the claimed isolated aggrecan peptide fragment. The examiner respectfully disagrees for reasons of record as supplemented below.

As stated in the previous Office Action, Antonsson et al. teach a peptide comprising amino acids 1-40 of SEQ ID NO: 3 (see enclosed alignment). The claim as amended does not obviate the rejection since the claim still recites the phrase "comprising a sequence of amino acids". Thus, the reference teaching anticipates claim 7 which is directed toward a peptide comprising a sequence that is at least 80% identical to amino acids 1-40 of SEQ ID NO: 3.

Claim Rejections - 35 U.S.C. § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 2, 8, 9, 11-14, 17-21, 31, and 32 stand rejected under 35 U.S.C. 103(a) as being

unpatentable over Fosang et al. (FEBS Lett. 1996 Feb 12;380(1-2):17-20; reference of record) in view of Koritsas et al. (Anal Biochem. 1995; 227: 22-26; reference of record).

Applicants' arguments filed 11/16/2005 have been fully considered but are not persuasive. Applicants' position is that the combination of references of Fosang et al. and Koritsas et al. do not teach each and every limitation of the amended claims and that the combination of these reference do not render obvious the subject matter of the claims. The examiner respectfully disagrees for reasons of record as supplemented below.

The teachings of each reference stated in the previous Office Action are reproduced here.

The teachings of Fosang et al. have been stated above. Fosang et al. does not teach a biotinylated peptide substrate.

Koritsas et al. teach methods for attaching biotin to gelatin comprising contacting gelatin with biotinyl-N-hydroxysuccinimide ester, where the biotinylated gelatin is subsequently immobilized onto microtiter plates for use in a protease assay that is sensitive to all proteolytic classes tested (see entire publication, especially p.23, left column, section *Preparation of biotinylated Gelatin*)

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to biotinylate the aggrecan G1-G2 peptide substrate taught by Fosang et al. by contacting biotinyl-*N*-hydroxysuccinimide ester as taught by Koritsas et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to have a protease substrate that can be used in the protease assay taught by Koritsas et al., where the assay is sensitive to all proteolytic classes tested.

Since lysine residues are present in the N- and C-terminal of the peptide taught by Fosang et al., then they would be inherently biotinylated at these regions (see GenBank Accession NP_037359 and NP_001126).

Subjecting the aggrecan G1-G2 peptide to a specific ADMP would result in proteolytically cleaved peptides comprising amino acid from the N-terminus through P1 of the ADMP-susceptible cleavage bond and proteolytically cleaved peptides comprising amino acid from the P1' of the ADMP-susceptible cleavage bond through C-terminus. Since the biotinylated substrate would be cleaved by a specific ADMP, then the cleaved peptide fragments would by still be biotinylated at specific lysine residues. Furthermore, it is within the purview of one of skill in the art to esterify of replace the P1 amino acid Glu as recited in claims 31 and 32 in order to prevent proteolytic hydrolysis of the substrate peptide.

Although the claims now recite "An isolated peptide fragment", this does not obviate the rejection. The said aggrecan G1-G2 peptide substrate taught by Fosang et al. is the isolated N-terminal fragment of cartilage proteoglycan protein core that was obtained after mild trypsin digestion of purified proteoglycan aggregates (see reference number [34]: Fosang et al. Biochem. J. (1989) 261, 801-809 (this reference is attached to the instant office action)). Thus,

the combination of Fosang et al. and Koritsas et al. teach every limitation of the amended claims and render obvious the subject matter recited in the amended claims.

20. Claims 10, 22, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fosang et al. in view of Koritsas et al. as applied to claims 2, 8, 9, 11-14, 17-21, 31, and 32 above, and further in view of Duan et al. (Anal Biochem. 1994 Feb 1;216(2):431-8).

Applicants' arguments filed 11/16/2005 have been fully considered but are not persuasive. Applicants' position is that the combination of references of Fosang et al., Koritsas et al., and Duan et al. does not teach each and every limitation of the amended claims and that the combination of these references does not render obvious the subject matter of the claims. The examiner respectfully disagrees for reasons of record as supplemented below.

The teachings of each reference stated in the previous Office Action are reproduced here.

Duan et al. teach method for adding the chromophore FTC (fluoresceinylthiocarbamyl) to peptides for use in assaying protease activity (see entire publication, especially pp. 431-433).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add the chromophore FTC taught by Duan et al. to the aggrecan G1-G2 peptide substrate taught by Fosang et al.. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to have a protease substrate that can be used in the protease assay taught by Duan et al.

Although the claims now recite "An isolated peptide fragment", this does not obviate the rejection. The said aggrecan G1-G2 peptide substrate taught by Fosang et al. is the isolated N-terminal fragment of cartilage proteoglycan protein core that was obtained after mild trypsin digestion of purified proteoglycan aggregates (see reference number [34]: Fosang et al. Biochem. J. (1989) 261, 801-809 (this reference is attached to the instant office action)). Thus, the combination of Fosang et al., Koritsas et al., and Duan et al. teaches every limitation of the amended claims and renders obvious the subject matter recited in the amended claims.

Conclusion

21. Claims 3, 5, 6, 24, 25 are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to

reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

23. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CLF

TEKCHAND SAIDHA
PRIMARY EXAMINER